Status and Problems of Receptor Mapping

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APPLICATION OF RADIORECEPTOR ASSAY (RRA).
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Radioreceptor assay (RRA) is a competitive radioassay based on interaction of labeld ligand with specific receptor sites in target cells. RRA has been used for measurement of hormones, growth factors, and their antagonists or agonists. In addition, RRA provides a useful tool for study of structure-function relationship of biologically active substances and for analysis of the receptors. The technique will be applicable to in vivo studies. In general, RRA is performed using subcellular fraction containing receptors of interest. However, kinetics in binding of labeled ligand to subcellular fractions is not identical with that seen in intact cells. When cultured cells are incubated with labeld peptide hormone such as insulin, ligand-bound receptor complex is internalized as a function of time and temperature. The internalized ligand is degraded by lysosomal enzymes and the degraded materials are released into extracellular space. Receptor-mediated degradation of labeled ligand is inhibited by lysosomotropic agents such as chloroquine. It is likely that binding and subsequent processing of labeld ligands given in vivo is different from those in vitro. Binding of labeld ligand to target cells or tissues in vivo may be affected by a number of factors such as transport or distribution of the labeld ligand, its degradation in other tissues and plasma proteins.

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LIGANDS LABELED WITH POSITRON EMITTERS-PRESENT STATUS.
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The study of neurotransmitter and drug receptors in the living brain has been made possible by the recent development of radioligands labeled with positron emitting radionuclides, permitting the external detection and quantification of receptor sites by PET. The status of the rapidly developing field of radioligand synthesis is reviewed and probable future development in this field is also discussed.

The most important requirement in the choice of radioligand, labeled at sufficiently high specific activity, is that the ligand exhibits a high degree of specific binding to receptors of interest in vivo and that is metabolically stable within brain tissue. Additional aspects include blood-brain permeability and biodistribution of the tracer. The choice and position of the radionuclide for preparing the radioligands, although there are constraints imposed by radiochemical synthetic routes within a limited number of labeled precursors, are also important for the selection process, depending on time course of the biological process and/or specific activity required.

Currently,potentially attractive tracers for such studies include [F-18]spiroperidol, [F-18] or [C-11]-N-methylspiroperidol, [C-11]raclopride, [C-11]SCH 23390, [C-11] suriclone, [C-11]RO 15-1788, [F-18]cyclofoxy and [C-11]carfentanil. Most of [C-11] ligand preparation have been achieved by N-methylation using readily available [C-11] methyl iodide. Only method that F-18 can be introduced into organic molecules in the NCA state is based on the nucleophilic substitution reactions. F-18 as a label may be preferrable especially when the ligand-receptor kinetics measurement is required.

There is still a need for the development of a high-yield and one-pot method of high specific activity radioligands. Although the cost and availability of short-lived positron emitters preclude widespread use, receptor mapping and studies of ligand-receptor kinetics with PET now open one of the most exciting way in methodology for the biochemical study of brain function.